Remarks

Claims 1-42 were pending in the subject application. By this Amendment, claims 1-4, 6-9, 11, 12, 18, 20, 21, and 23-29 have been amended, claims 5, 10, 13, 16-17, 22, and 32-42 have been cancelled, and new claims 43-57 have been added. The undersigned avers that no new matter is introduced by this amendment. Entry and consideration of the amendments presented herein is respectfully requested. Accordingly, claims 1-4, 6-9, 11, 12, 14, 15, 18-21, 23-31, and 43-57 are currently before the Examiner for consideration. Favorable consideration of the pending claims is respectfully requested.

Submitted herewith is an Information Disclosure Statement (IDS), accompanied by the form PTO/SB/08 and copies of the references listed therein. The applicant respectfully requests that the references listed on the form PTO/SB/08 be considered and made of record in the subject application.

By this Amendment, claim 1 has been amended to recite administration of an effective amount of a nucleic acid sequence encoding IL-12, and an operably linked promoter sequence; and an effective amount of a nucleic acid sequence encoding IFN-γ, and an operably linked promoter sequence. Support for this amendment can be found, for example, at page 2, lines 27-29; page 3, lines 1-3; page 5, lines 21-23; page 7, lines 28-29, and page 9, lines 10-11, of the subject specification. By this Amendment, claim 1 has also been amended to recite that administration of the nucleic acid sequences results in an increase of Th1-type cytokine production and a decrease of Th2-type cytokine production within the patient. Support for this amendment can be found, for example, at page 6, lines 2-4 and 20-24, of the subject specification. Support for the amendment to claims 2 and 21 can be found, for example, at page 13, lines 24-30, pages 14-16, page 17, lines 1-16, and the claim as originally filed. Support for the amendments to claims 3, 4, and 6-8, can be found, for example, at page 5, lines 1-14, and pages 13-17 of the subject specification. Claims 9 and 18 have been amended for consistency. Claim 11 has been amended to recite that the nucleic acid sequences are administered within separate DNA plasmids. Support for this amendment can be found, for example, at page 7, lines 28-29; page 9, lines 28-29; and page 10, lines 1-3, of the subject specification. Support for the amendment to claim 12 can be found, for example, at page 8, lines 17-

29; and page 9, lines 1-16, of the subject specification. Claim 20 has been amended to recite that the composition comprises a nucleic acid sequence encoding IL-12, and an operably linked promoter sequence; and a nucleic acid sequence encoding IFN-γ, and an operably linked promoter sequence. Support for this amendment can be found, for example, at page 2, lines 27-29; page 3, lines 1-3; page 5, lines 21-23; page 7, lines 28-29, and page 9, lines 10-11, of the subject specification. Support for the amendments to claims 23-26 can be found, for example, at page 5, lines 1-14, and pages 13-17 of the subject specification. Claim 27 has been amended for consistency. Claim 28 has been amended to recite that the nucleic acid sequences are contained within separate DNA plasmids. Support for the amendment to claim 28 can be found, for example, at page 7, lines 28-29; page 9, lines 28-29; and page 10, lines 1-3, of the subject specification. Support for the amendment to claim 29 can be found, for example, at page 8, lines 17-29; and page 9, lines 1-16, of the subject specification.

By this Amendment, claims 43-57 have been added. Support for claims 43-57 can be found, throughout the subject specification as filed. Support for claim 43 can be found, for example, at page 2, lines 27-29; page 5, lines 21-23; page 6, lines 2-5; page 7, lines 28-29; page 9, lines 1-11; and page 10, lines 1-2, of the subject specification. Support for claim 44 can be found, for example, at page 3, lines 2-3; and page 5, lines 18-21, of the specification. Support for claim 45 can be found, for example, at page 7, lines 12-13, of the specification. Support for claim 46 can be found, for example, at page 7, lines 12-13, of the specification. Support for claim 47 can be found, for example, at page 22, lines 21-27; and page 24, lines 22-25, of the specification. Support for claim 48 can be found, for example, at page 7, lines 12-13; page 22, lines 21-27; and page 24, lines 22-25, of the specification. Support for claim 49 can be found, for example, at page 11, lines 28-29, of the specification. Support for claim 50 can be found, for example, at page 5, lines 1-14, and pages 13-17 of the subject specification. Support for claim 51 can be found, for example, at page 25, lines 10-15, of the specification. Support for claim 52 can be found, for example, at page 6, lines 12-14, of the specification. Support for claim 53 can be found, for example, at page 3, lines 2-3; and page 12, lines 4-8, of the specification. Support for claim 54 can be found, for example, at page 2, lines 27-29; page 5, lines 21-23; page 6, lines 2-5; page 7, lines 28-29; page 9, lines 1-11; and page 10, lines 1-2 and 4-10 of the subject specification. Support for claim 55 can be found, for example, at page 3, lines 2-3; and page 5, lines 18-21, of the specification. Support for claim 56 can be found, for

example, at page 7, lines 12-13, of the specification. Support for claim 57 can be found, for example, at page 5, lines 1-14, and pages 13-17 of the subject specification.

As an initial matter, the Examiner has requested that the applicants should indicate in a Cross-Reference to Related Application section that the subject application claims the benefit of U.S. Provisional Application No. 60/319,523. The applicants respectfully submit that a Cross-Reference to Related Application section is present at page 1, lines 6-10, of the specification, which includes a reference to provisional Application No. 60/319,523, filed September 5, 2002. Accordingly, reconsideration and withdrawal of this objection is respectfully requested.

The Examiner has objected to the specification for reciting that SEQ ID NO:9 is the nucleotide sequence of the human IL-12 p49 subunit. The specification has been amended to recite that SEQ ID NO:9 is the nucleotide sequence of the human IL-12 p40 subunit. Support for this amendment can be found, for example, at page 14, lines 29-42, and page 15, lines 1-30, of the specification. Accordingly, reconsideration and withdrawal of this objection is respectfully requested.

Claims 1-15, 18-31, and 34-39 have been rejected under 35 U.S.C. §112, first paragraph, as lacking sufficient written description. The applicants respectfully submit that the specification provides an adequate written description of the claimed subject matter. However, the applicants have amended the claims to expedite prosecution of the subject application. By this Amendment, the applicants have amended claim 1 to clarify that administration of the nucleotide sequence results in an increase of Th1-type cytokine production and a decrease of Th2-type cytokine production within the patient. Likewise, new claim 43 recites that administration increases Th1-type cytokine production and decreases Th2-type cytokine production. The claims no longer recite biologically active fragments or homologs. The applicants respectfully submit that the specification conveys to one of ordinary skill in the art that the applicants were in possession of the claimed subject matter at the time the application was filed. Accordingly, in view of the foregoing remarks, the applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. §112, first paragraph.

Claims 1-15, 18-31, and 34-39 have been rejected under 35 U.S.C. §112, first paragraph, as non-enabled by the subject specification. The applicants respectfully submit that the claims are fully enabled by the subject specification.

The Office Action indicates that the specification does not reasonably enable a method for modulating any and all immune responses. As indicated above, the applicants have amended claim 1 to clarify that modulation of the immune response, in accordance with the subject invention, involves an increase of Th1-type cytokine production and a decrease of Th2-type cytokine production within the patient. As acknowledged at page 6 of the Office Action, the working examples in the subject specification demonstrate that administration of nucleic acids encoding IL-12 and IFN-gamma to mice increases Th1-like cytokine levels and decreases Th2-like cytokine levels, among other immunological effects, such as inhibiting IgE production and increasing IgG2a production. Further, by this Amendment, the applicants have amended the claims to remove reference to biological fragments and homologs of IL-12 and IFN-γ.

The Office Action indicates that the subject specification does not teach or contemplate the construction of a single nucleic acid encoding both IL-12 and IFN-gamma, or biologically active fragments or homologs thereof. As taught at page 7, lines 28-29, of the subject specification, in accordance with the subject invention, the IL-12-encoding nucleic acid sequence and IFN-gamma-encoding nucleic acid sequence can be within the same nucleic acid molecule or separate nucleic acid molecules. Furthermore, as taught at page 8, lines 1-4, of the specification, multimers (repeating units) of IL-12-encoding nucleic acid sequences and/or IFN-gamma-encoding nucleic acid sequences (homopolymers or heteropolymers) may be used for enhanced expression. The applicants respectfully submit that fusions of coding sequences are well known in the art. However, the applicants have amended the claims to expedite prosecution of the subject application. By this amendment, the applicants have amended claim 1 to recite that a nucleic acid sequence encoding IL-12 and a nucleic acid sequence encoding IFN-γ are administered. Claim 20 recites that the pharmaceutical composition comprises a nucleic acid sequence encoding IL-12 and a nucleic acid sequence encoding IFN-γ, with operably linked promoters.

The Office Action indicates that the specification does not provide an enabling disclosure for using any expression vector/promoter combination. The applicants submit that the scope of the

claims is commensurate with the teachings of the specification. The applicants respectfully submit that the art of gene delivery has advanced significantly since 1995-1997 (the time period in which the Verma *et al.* and Orkin *et al.* references were published) and the filing date of the subject application.

New claim 43 recites that an effective amount of a plasmid comprising a nucleic acid sequence encoding IL-12 and an effective amount of a plasmid comprising a nucleic acid sequence encoding IFN-γ are administered to the patient. New claim 54 recites a pharmaceutical composition comprising a plasmid comprising a nucleic acid sequence encoding IL-12 and a plasmid comprising a nucleic acid sequence encoding IFN-γ. It is noted that the Office Action acknowledges that the specification enables a method for inhibiting IgE production, increasing IgG2a production, producing more Th-2 like cytokines, and less Th2-like cytokines by administering separate plasmids encoding IL-12 and IFN-γ operably linked to cytomegalovirus (CMV) promoter sequences. With respect to the promoter sequence, the applicants respectfully submit that selection of promoters capable of directing expression of the IL-12 and IFN-γ coding sequences is well within the skill of those of ordinary skill in the art. It is well settled that the specification need not disclose what is well-known to those skilled in the art and preferably omits that which is well-known to those skilled and already available to the public. *In re Buchner*, 929 F.2d 660, 661; 18 USPQ2d 1331, 1332 (Fed. Cir. 1991); *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384; 231 USPQ 81, 94 (Fed. Cir. 1986), cert. denied, 480 U.S. 947 (1987); and *Lindemann Maschinenfabrik GMBH v. American Hoist & Derrick Co.*, 730 F.2d 1452, 1463; 221 USPQ 481, 489 (Fed. Cir. 1984). Accordingly, in view of the foregoing remarks, the applicant respectfully requests reconsideration and withdrawal of the rejection under 35 U.S.C. §112, first paragraph.

Claims 14, 15, and 31 have been rejected under 35 U.S.C. §112, first paragraph, as non-enabled by the subject specification. The applicants respectfully submit that the claims are fully enabled by the subject specification.

The Office Action indicates that "the specification only teaches the administration of a rough KBG allergen extract to mice prior to or in conjunction with administration of plasmid encoded IL-12 and IFN-γ" (page 9, second full paragraph of the Office Action). The applicants respectfully submit that the applicants' specification is improperly interpreted as being limited to its working examples. Guidance concerning the antigen is provided at page 7, lines 2-27, of the subject

specification. The Office Action indicates that "not all carbohydrates are capable of inducing an immune response" (page 9 of the Office Action). The applicants respectfully submit that, by definition, a carbohydrate antigen is capable of inducing an immune response. One of ordinary skill in the art would appreciate that various antigens, in addition to Kentucky blue grass (KBG) extract, could be used with the subject invention. Whole extracts can be used in immunotherapy. For example, allergens for dust mite, cat, dog, weed, grass, nuts, latex, and tree are commercially available. Furthermore, the specification teaches that administration of the nucleic acid sequences encoding the IL-12 and IFN-γ results in an increase of Th1-type cytokine production and a decrease of Th2-type cytokine production within the patient, which provides those of ordinary skill in the art with further guidance for selection of an antigen to be administered with the nucleic acid sequences. New claims 45 and 56 recite that the antigen is an allergen.

Accordingly, in view of the foregoing remarks, the applicant respectfully requests reconsideration and withdrawal of the rejection under 35 U.S.C. §112, first paragraph.

Claims 1-15, 18-31, and 34-39 have been rejected under 35 U.S.C. §112, second paragraph, as indefinite. The applicants respectfully submit that the claims are not indefinite. However, by this Amendment, claim 1 has been amended to clarify that the recited modulation of an immune response includes an increase of Th1-type cytokine production and a decrease of Th2-type cytokine production within the patient. The term "biologically active fragments" has been removed from the claims. Accordingly, reconsideration and withdrawal of the rejection under 35 U.S.C. §112, second paragraph, is respectfully requested.

Claims 1-10, 12-14, 20-29, 34-36, 38, and 39 have been rejected under 35 U.S.C. §103(a) as being obvious over Hogan *et al.* (*Eur. J. Immunol.*, 1998, 28:413-423) in view of Li *et al.* (*J. Immunol.*, 1996, 157:3216-3219) and further in view of Carroll *et al.* (*J. of the Nat. Canc. Inst.*, 1998, 90:1881-1887). The applicants respectfully submit that the claimed invention is not obvious over the cited references.

The specification teaches, and claim 1 now recites, that administration of a nucleic acid sequence encoding IL-12 and a nucleic acid sequence encoding IFN-γ effectively increases Th1-type cytokine production and decreases Th2-type cytokine production. The cited references provide no reasonable expectation of achieving this result. Moreover, as indicated at page 30, lines 3-4, of the

subject specification, and shown in Figure 3C, administration of plasmids encoding IL-12 and IFN-γ resulted in a synergistic shift in cytokine profile. Specifically, Th1-type cytokine production was increased and Th2-type cytokine production was decreased. Figure 3C is a graph showing an analysis of the dominant cytokine pattern after cytokine DNA vaccination in a mouse model. To examine the dominant pattern of cytokine responses, IFN-γ/IL-4 and IL-2/IL-4 ratios were compared among different groups of mice. The results indicate that the net cytokine balance shifted in favor of the Th1-like response in cytokine-vaccinated mice; however, this shift was significantly greater in the group vaccinated with the combination of IFN-γ and IL-12. Moreover, Figure 3C shows that the ratio of IFN-γ/IL-4 was increased beyond what would be expected from the additive effects of IL-12 and IFN-γ, individually.

It is well settled in patent law that "a greater than expected result is an evidentiary factor pertinent to the legal conclusion of obviousness ... of the claims at issue" *In re Corkill*, 226 USPQ 1005 (Fed. Cir. 1985). Evidence of a greater than expected result may be shown by demonstrating an effect which is greater than the sum of each of the effects taken separately (*i.e.*, demonstrating "synergism"). *Merck & Co. Inc. v. Biocraft Laboratories Inc.*, 10 USPQ2d 1843 (Fed. Cir.), *cert. denied*, 493 U.S. 975 (1989).

The benefits of the claimed method and compositions are unexpected in view of the cited references, and have a significant, practical advantage for immunotherapy. Therefore, the applicants respectfully submit that the claimed invention is not obvious over the prior art.

The applicants note that the Office Action indicates that claims 11, 15, 19, 30, 31, and 37 are free of the prior art of record. The applicants respectfully submit that claims 43-57, which are added by this Amendment, are non-obvious over the cited references. New claim 43 recites a method for modulating an immune response comprising administering an effective amount of a plasmid comprising a nucleic acid sequence encoding IL-12, and an operably linked promoter sequence; and an effective amount of a plasmid comprising a nucleic acid sequence encoding IFN-γ, and an operably linked promoter sequence, resulting in an increase of Th1-type cytokine production and a decrease of Th2-type cytokine production within the patient. New claim 54 recites a pharmaceutical composition comprising a plasmid comprising a nucleic acid sequence encoding IL-12, and an

operably linked promoter; a plasmid comprising a nucleic acid sequence encoding IFN-γ and an operably linked promoter; and a pharmaceutically acceptable carrier.

In view of the foregoing remarks, reconsideration and withdrawal of the rejection under 35 U.S.C. §103(a) is respectfully requested.

In view of the foregoing remarks and amendments to the claims, the applicants believe that the currently pending claims are in condition for allowance, and such action is respectfully requested.

The Commissioner is hereby authorized to charge any fees under 37 C.F.R. §§ 1.16 or 1.17 as required by this paper to Deposit Account 19-0065.

The applicants invite the Examiner to call the undersigned if clarification is needed on any of this response, or if the Examiner believes a telephonic interview would expedite the prosecution of the subject application to completion.

Respectfully submitted,

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